Clinical Research

Economic Evaluation of Treatment Strategies for Patients Suffering Acute Myocardial Infarction in Greece

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Economic evaluation, cost-effectiveness analysis, acute myocardial infarction, thrombolytic drugs.

Introduction: Acute myocardial infarction (AMI) is one of the leading causes of death in Greece and elsewhere. The objective of this paper was to conduct an economic evaluation of three alternative treatment options, alteplase, reteplase, and tenecteplase, in different groups of patients.

Methods*:* A systematic review of the literature was undertaken to identify studies evaluating the three treatments considered. Data from selected trials were extracted and applied to a decision analytic model, which has a time horizon extending to the end of a patient's life. The health outcomes included in the analysis contain all major health events that may occur after an AMI. Total treatment cost comprises the cost of initial treatment, the cost associated with hospitalisations due to AMI and events such as stroke, reinfarction, etc., and the lifetime costs of patients surviving. The model allows for different patient sub-groups. Simulation was used to test the robustness of the findings.

Results: For the baseline group, there was no major difference between the three treatments, in terms of treatment cost and survival. Specifically, lifetime cost per patient was around €18,950 (range €18,947 - €18,990) and overall survival was around 8.4 years (range 8.359 - 8.472). Nonetheless, for patients above the age of 75 and for patients starting treatment 4 hours after symptom onset, tenecteplase was more cost-effective compared to the other two treatments. Its incremental cost effectiveness ratio was €2,205 in the former group and €868 in the latter and these results reached high levels of significance.

Conclusion: Despite its higher price, in the setting of the Greek National Health Service tenecteplase is a cost-effective treatment for AMI patients, comparable to alteplase and reteplase, and it should also be included in the positive drug list along with the other two drugs. Simple price comparison of alternative treatments is not the best option for supporting decisions on pricing and reimbursement of new therapies.

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Despite declining trends in recent years, coronary heart disease remains the leading cause of life loss and suffering in most developed countries. One of its main manifestations is acute myocardial infarction (AMI), which in most cases is the outcome of a thrombus or clot forming on top of a ruptured atherosclerotic plaque, blocking the blood flow through the artery. Unless the blood flow can be quickly restored, the muscle supplied by that artery "infarcts", or dies because of lack of oxygen, and this may cause heart failure, fatal heart rhythm disturbances and death. The onset of symptoms is usually sudden and the highest risk of death is within the first hour of experiencing an AMI. International data show that almost a third of patients experiencing AMI die within the first hour of the onset of symptoms and that thirty-day or

year fatality rates for AMI reach as high as 50%.[1-4] The disease also generates a substantial economic burden on health care systems, mainly due to pharmaceuticals and hospital care, and society overall, in terms of productivity losses.[5-7]

The standard approach to the management of AMI is to dissolve the clot by mechanical (angioplasty) or chemical means. Recent evidence suggests that early delivered angioplasty has advantages, but this kind of treatment is not always readily available and hence thrombolysis represents the most commonly used approach, though often angioplasty may follow. The earlier the use of a thrombolytic agent after the onset of symptoms, the higher the chance for survival.[1,8-11]

Alteplase is an early generation fibrinolytic agent, very similar to the naturally occurring activator of plasminogen in the human body, and it is delivered in a bolus dose followed by infusion over 90 minutes. Reteplase is a more recent drug, a recombinant plasminogen activator similar to alteplase, but with a prolonged half-life, delivered through two IV bolus injections 30 minutes apart. Tenecteplase is the most recently introduced in Greece and elsewhere. It is a recombinant plasminogen activator similar to alteplase, but with a prolonged half-life, increased fibrin specificity and increased resistance to inhibition by plasminogen activator inhibitors. It is administered through a single IV bolus injection.

The profiles (mode of delivery, action, and clinical data) of these thrombolytic treatments and their prices are somewhat different and various economic evaluations have attempted to compare their cost-effectiveness.[12-20] However, only one of them considered tenecteplase and none was conducted in the setting of a Greek National Health Service (NHS) hospital. A recent review by the National Drug Agency left tenecteplase outside the drug positive list, because its price was marginally higher relative to alteplase and reteplase, which were already included. The "value" of new treatments, though, is not necessarily reflected in simple price comparisons and more holistic approaches are necessary in order to make decisions as to whether, when, how and with whom we should use alternative treatment options. Simple price comparisons represent a very confined and often diluted view of things and should be avoided for decision making.

Thus, an economic evaluation was undertaken from the perspective of the Greek NHS to compare the cost-effectiveness of the new agent, tenecteplase, relative to the ones already included in the reimbursement list, reteplase and alteplase, in different patient groups.

Methods

Drug dosages

The doses considered were as follows: alteplase 100 mg given in the accelerated manner, namely 50 mg in bolus and the rest by infusion over 90 minutes; reteplase in two bolus doses of 5 units per dose half an hour apart; tenecteplase in one dose over 5 minutes with an IV bolus injection. We also consider that the standard of care requires that aspirin and heparin be co-administered.

Analytical method and health outcomes

Direct comparisons of the three agents within randomised controlled trials are not available. Also, the evidence concerning treatment effectiveness comes from short run, 30-day clinical trials, although the implications follow patients throughout their remaining lifetime. Additionally, even though the main treatment outcome is survival, there are several other important health outcomes that may occur post AMI and these are characterised by different economic implications, while there are also significant differences in the event rates between alternative treatments. For all these reasons we used the model presented in figure 1: after the occurrence of an AMI and the delivery of treatment, patients may survive without any further complications; they may survive, but with occurrence of an event such as reinfarction, stroke, bleeding etc.; or they may die. These events were selected on the basis of literature review, as well as expert advice, and have economic implications.

Event rates

The event rates used to populate the model were derived from trial data which were found from a systematic review of the literature. Search terms used included myocardial infarction, heart infarction, thrombolysis and other related terms, combined with the specific drug terms. The search included: Medline, Embase, Science Citation Index, Cochrane Trials Register, the Health Technology Assessment and the NHS Economic Evaluation Database, the Database of Abstracts of Reviews of effectiveness, and internet sites such that of the National Institute of Clinical Excellence in the UK. Studies were assessed for their quality on the basis of standard accepted criteria in respect of randomisation, baseline comparability, inclusion and exclusion criteria, blinding, and manage-

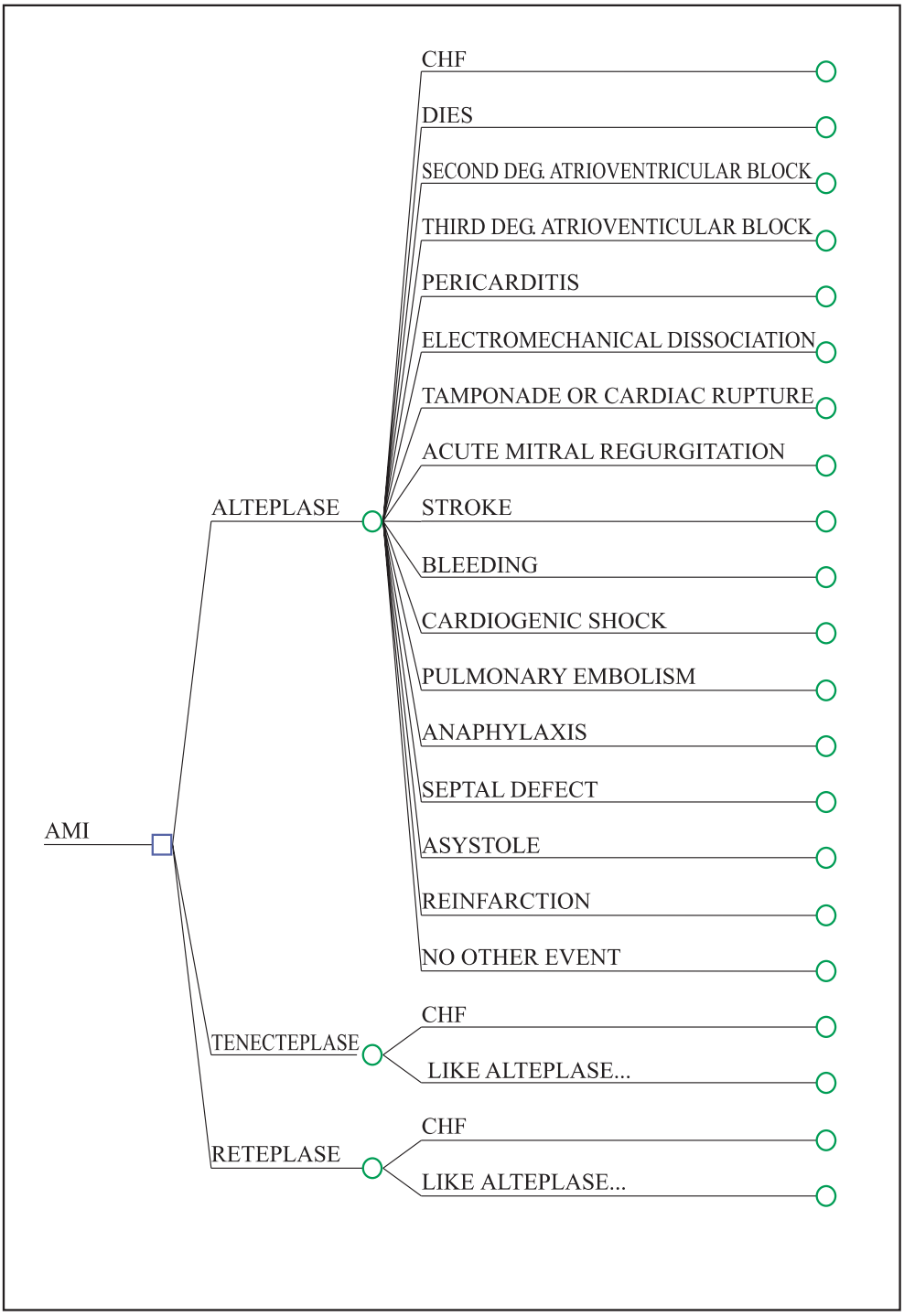

Figure 1. Decision tree of AMI treatment. CHF – congestive heart failure.

ment of withdrawals.[21] The focus was on the drugs considered in the evaluation, on hospital settings, on large phase III randomised controlled trials and the health outcomes of interest. Through this process we ended up with two large multinational trials, one comparing alteplase with reteplase[22] and the other alte-

Table 1. Characteristics of trial populations.

	ASSENT – 2		GUSTO III	
	Alteplase	Tenecteplase	Alteplase	Reteplase
Patients	8,488	8,461	4,921	10,138
Age	61 (51-70)	62 (52-70)	63 (53-72)	63 (53-71)
> 70-75 %	12.6	12.7	13.5	13.6
Female %	23.3	22.9	27.2	27.5
Time to treatment (hours)	2.8 (1.9-3.8)	2.7 (1.9-3.8)	2.7 (1.9-3.9)	2.7 (1.8-3.8)
Previous MI %	16.1	15.8	18.4	18.4
Follow up	30 days	30 days	30 days	30 days
Blood pressure (mmHg)	133 (119-150)	133 (120-150)	134 (119-150)	135 (119-150)

plase with tenecteplase.[23] Data were extracted by two independent researchers using a common questionnaire.

The reference population and the reference set of event rates is that of alteplase as reported in GUSTO III.[22] As shown in table 1, the two trials recruited quite similar populations with respect to demographics and main clinical characteristics. Nonetheless, in the model, the event rates of the two other drugs are based on their relative risks in relation to alteplase, obtained from GUSTO III in the case of reteplase and from ASSENT 2 in the case of tenecteplase.[22,23] Hence, one avoids the problem of non-identical populations and has only to assume that the relationship between drugs, i.e. the relative risk, observed in the one population would be the same in the other trial population—a safe assumption here in light of the similarity of the populations and the trial designs. Using this structure also makes it easy to compute evaluations for subgroups of patients with different age, sex, and time to treatment. Baseline probabilities and relative risks are presented in table 2.

Additionally, the two trials used to build the model report results for different subgroups, especially for those above the age of 75 and for those to whom treatment was given more than 4 hours after symptom onset. In the elderly the event rates increase substantially: death rates associated with alteplase reported from GUSTO III reached 20.2%, bleeding 9.23% and stroke 3.9%. In this group tenecteplase showed a relative risk for death of 0.903 (LCI: 0.754, UCI: 1.081). In a similar fashion, the death rate for alteplase in patients who started treatment more than 4 hours after symptom onset was 9.2%; the relative risk of reteplase was 1.228 and that of tenecteplase 0.766 (LCI: 0.617, UCI: 0.952), a statistically significant reduction.

Analytical horizon

The trials mentioned above report thirty day outcomes, but AMI has lifetime health and economic implications for sufferers. Data from the one-year follow up of the studies were combined with evidence about long term survival of AMI patients and were then applied to Greek life tables from the Greek census of registry to extrapolate the results to the end of the patients' lifetime.[24-26] Hence, for the reference group containing patients with an average age of 63 who survived an AMI without any further complications, we assumed that they would live on average for another ten years, whilst if they experienced complications such as stroke, reinfarction or bleeding, they would live on average for eight more years. We also carried out an analysis limited to one year only, so that no extrapolation was necessary because trial follow up data were available. Both costs and life expectancy were discounted at 3.5% at the baseline scenario, but other rates were tested in the sensitivity analysis.

Costing

Total patient cost is an aggregate of three major components: the cost of the thrombolytic agent and the materials used to deliver it, the cost of in-hospital stay and, after discharge, the cost of maintenance for the remaining lifetime. The cost of in-hospital treatment depends upon the event and was estimated from an analysis of electronic patient records, from 1996 to 2002, obtained from the information system of the General University Hospital of Patras, one of the largest hospitals in Greece, which treated approximately 1,200 AMI cases during the period in question. The cost of maintenance was estimated on the basis of expert advice and reflects

Table 2. Event rates and relative risks

Event	Probability of Alteplase *	Relative Risk of Tenecteplase **	Relative Risk of Reteplase
Death	6.15 (0.34)	0.992 (0.05)	1.032 (0.07)
Stroke	1.66 (0.16)	1.074 (0.14)	0.916 (0.14)
Bleeding	5.94 (0.48)	0.784 (0.15)	1.015 (0.10)
Anaphylaxis	0.2 (0.02)	0.376 (0.04)	0.833 (0.01)
Congestive heart failure	17.5 (1.36)	0.872 (0.08)	0.983 (0.09)
Reinfarction	3.81 (0.29)	1.078 (0.09)	1.000 (0.09)
Cardiogenic shock	4.00 (0.31)	0.965 (0.07)	1.045 (0.10)
Tamponade or cardiac rupture	7.00 (0.05)	0.816 (0.19)	0.889 (0.08)
Pericarditis	2.60 (0.20)	1.124 (0.11)	1.000 (0.10)
Acute mitral regurgitation	0.7 (0.05)	0.886 (0.20)	1.500 (0.15)
Ventricular septal rupture	3.00 (0.02)	0.817 (0.03)	0.667 (0.06)
Pulmonary embolism	0.04 (0.00)	2.750 (0.20)	1.000 (0.10)
Second degree atrioventricular block	2.20 (0.17)	1.000 (0.10)	1.273 (0.12)
Third degree atrioventricular block	3.1 (0.24)	1.000 (0.10)	1.129 (0.11)
Asystole	4.2 (0.03)	1.000 (0.10)	1.000 (0.1)
Electromechanical dissociation	2.2 (0.17)	1.000 (0.04)	1.091 (0.11)

*Derived from GUSTO III[22], ** Derived from ASSENT 2[23]. Figures in parentheses represent standard deviations.

the most commonly prescribed patterns of care at patient discharge. Table 3 presents, in Euro 2003 prices, the costs of thrombolytic agents, the medications given and the costs during the 7-day hospitalisation. It also includes information about the medications prescribed and the costs occurred after discharge during the patient's lifetime. The extra hospital costs of treating events such as stroke, asystole, bleeding, etc. are given in table 4.

Sensitivity analyses and subgroup analyses

Analyses and results are presented for the reference set of patients, that of GUSTO III, and for two important subgroups: those above the age of 75 and those for which treatment is initiated after 4 hours following symptom onset. Also, analysis was conducted for a time horizon of one year. To test the robustness and sensitivity of the results stochastic analysis was employed in the form of Monte Carlo simulation. In particular, baseline probabilities, relative risks and the cost data in the model were assigned normal distributions, with the means and standard deviations presented in the corresponding tables, and the results of 5,000 simulations were used to compute statistics for the key parameters of interest and acceptability curves, which show the probability that specific cost effectiveness ratios may hold true and be accepted.[27]

Results

The baseline patient group, evaluated in GUSTO III, refers to patients around 63 years of age, 14% of whom were above the age of 75, 27% of whom were women and whose risk profile was as follows: 40% had prior hypertension, 16% were diabetic, 41% were smokers, 35% had hypercholesterolaemia, 18% a prior infarction and 4% had undergone prior bypass surgery. Importantly, the median interval between onset of symptoms and treatment was 2.7 hours.

The results of the evaluation for the baseline group are presented in Table 5, which includes figures based on the roll out of the decision tree and also statistical information based on the results of 5,000 Monte Carlo simulations. Both costs and life years are discounted at 3.5%. In terms of life expectancy, tenecteplase was marginally better (8.472, mean: 7.122), followed by alteplase (8.402, mean: 7.096) and reteplase (8.359,

Table 3. Costs generated during hospitalisation and after discharge.

Type	Cost (€)
In hospital	
Alteplase	791
Reteplase	799
Tenecteplase	999
Aspirin 325 mg	0.1
Nitroglycerin IV 50mg	5.1 x 2 days
Clopidogrel 75 mg	1.33 x 7 days
Dobutamine	5 for 3 days
Atenolol	0.1 x 7 days
Isosorbide mononitrate 60mg	0.26 x 7 days
Atorvastatin	1.76 x 7 days
Furosemide	1.23 x 7 days
Heparin	25
Tirofiban	348
Coronary angiography	325 (for some patients)
Angioplasty	5,800 (for some patients)
Hospitalisation	280 for 7 days
After discharge	
Aspirin 325 mg	0.1 per day for lifetime
Clopidogrel 75 mg	1.33 per day for lifetime
Atenololo	0.1 per day for lifetime
Furosemide	1 per day for lifetime
Isosorbide mononitrate 60mg	0.26 per day for lifetime
Acenocumarol	5 for 3 days
Atorvastatin	5 for 180 days
Lipitor	1.76 for lifetime
Physician visits	5 twice per year
Rehabilitation for stroke patients	1,000 in first year

Table 4. Additional in-hospital costs of events

Event	Cost (€)
Stroke	1,300 (120)
Reinfarction	1,125 (134)
Congestive heart failure	561 (50)
Cardiogenic chock	2,730 (312)
Electromechanical dissociation	821 (56)
Tamponade or cardiac rupture	279 (56)
Second degree atrioventricular block	1,961 (112)
Third degree atrioventricular block	1,921 (156)
Asystole	1,921 (159)
Acute mitral regurgitation	2,415 (267)
Ventricular septal rupture	1,415 (123)
Anaphylaxis	300 (45)
Pulmonary embolism	2,050 (234)
Bleeding	1,200 (132)
Pericarditis	100 (8)
Death	1,200 (167)

Figures in parentheses represent standard deviations.

mean: 7.096), but none of the differences was statistically significant. The same applies for lifetime treatment costs where tenecteplase had a marginally higher cost (€18,990, mean: €18,144), followed by reteplase (€18,947, mean: €18,075) and then alteplase (€18,896, mean: €17,984); again none of the differences were statistically significant. Thus, according to our analysis, for the reference group under consideration one can not reject the hypothesis that the three treatments under consideration have equal effectiveness, lifetime patient costs and cost-effectiveness and for that reason on the basis of the above factors there is no apparent case to make distinctions between them.

Table 5 also presents results for the subgroup of patients above the age of 75. Again tenecteplase was associated with marginally higher cost (€12,784, mean: €11,939), followed by reteplase (€12,600, mean: €11,792) and then alteplase (€12,590, mean: €11,726) and these differences were statistically significant. This was also the case for life expectancy. Specifically, the life expectancy for tenecteplase was higher (1.536, mean: 1.569), followed by alteplase (1.448, mean: 1.499) and then reteplase (1.403, mean: 1.433). Thus, reteplase was inferior to alteplase, while the incremental cost-effectiveness of tenecteplase in relation to alteplase was €2,205 (mean: €3,043), a relatively low figure which argues for the use of the former treatment. Figure 2 depicts the cost-effectiveness acceptability curve of alteplase relative to reteplase and that of tenecteplase relative to alteplase, which show high levels of acceptance for tenecteplase in this group even at very low economic thresholds.

In addition, table 5 includes results for the group for which treatment was first delivered later than 4 hours after symptom onset. Similarly to the previous group, there were statistically significant differences in favour of alteplase and tenecteplase, with regard to both life expectancy and treatment costs. Reteplase was again in last place and the incremental cost per life year saved with tenecteplase relative to alteplase for the late treated patients was €868 (mean: €1,073), and reached high levels of acceptance even at low economic thresholds, as depicted graphically in figure 3.

The above results were confirmed in a number of additional analyses where other discounting rates were used and the basic assumptions and parameters of the model were altered. One-way sensitivity analysis showed that 10% changes in each of the parameters in the model (costs, events, relative risks, and basic as-

Table 5. Cost effectiveness analysis of thrombolytic agents.

	Reteplase		Alteplase		Tenecteplase	
	Total Cost	Life Years	Total Cost	Life Years	Total Cost	Life Years
Baseline group						
Expected	€ 18,947	8.359	€ 18,896	8.402	€ 18,990	8.472
Mean	€ 18,075	7.096	€ 17,984	7.096	€ 18,144	7.122
SD	€ 490	0.432	€ 456	0.362	€ 445	0.364
UCI	€ 19,036	7.944	€ 18,877	7.806	€ 19,015	7.836
LCI	€ 17,114	6.249	€ 17,091	6.386	€ 17,273	6.408
Elderly group above 75						
Expected	€ 12,600	1.403	€ 12,590	1.448	€ 12,784	1.536
Mean	€ 11,792	1.433	€ 11,726	1.499	€ 11,939	1.569
SD	€ 1,103	0.106	€ 1,143	0.089	€ 1,186	0.094
UCI	€ 11,822	1.435	€ 11,758	1.501	€ 11,972	1.572
LCI	€ 11,761	1.430	€ 11,694	1.496	€ 11,906	1.566
Patients starting treatment after 4 hours						
Expected	€ 18,599	7.864	€ 18,681	8.097	€ 18,924	8.377
Mean	€ 18,529	6.901	€ 18,640	7.112	€ 18,772	7.235
SD	€ 72	0.457	€ 4	0.598	€ 110	0.633
UCI	€ 18,531	6.913	€ 18,642	7.128	€ 18,775	7.252
LCI	€ 18,527	6.888	€ 18,639	7.095	€ 18,769	7.217

Results discounted at 3.5%. SD – standard deviation, UCI – 95% upper confidence interval, LCI – 95% lower confidence interval.

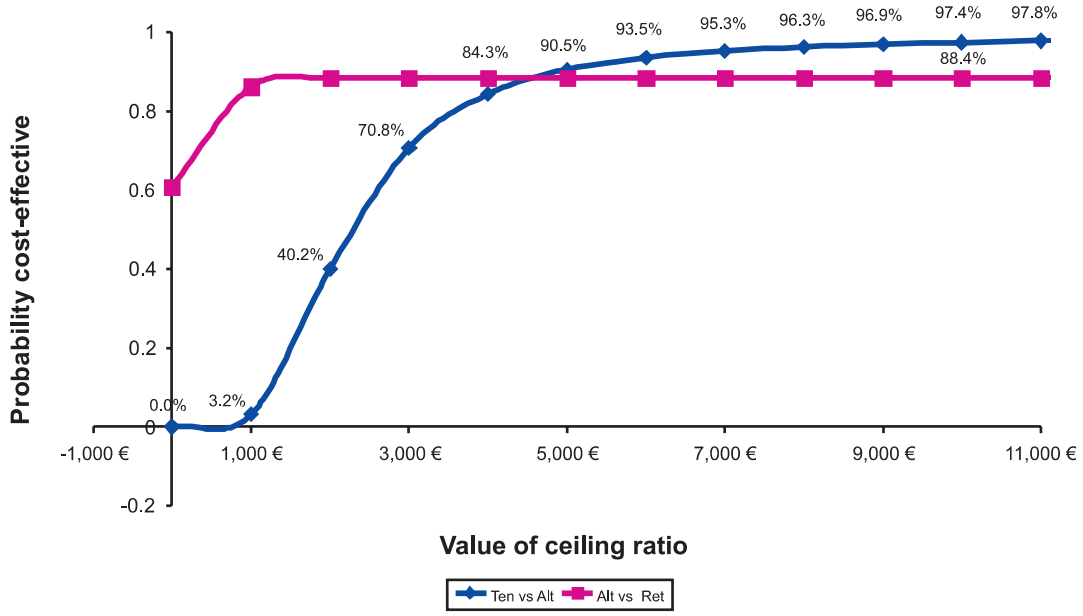

Figure 2. Cost effectiveness acceptability curve for elderly patients.

sumptions) had less than 2.5% impact at maximum on the cost and effectiveness results reported above and thus had no impact on the study conclusions. Finally, if we restrict the time period of the analysis to one year, then there were no statistical differences in survival and in the total treatment costs. With regard to the cost of treating patients, tenecteplase was associated with a marginally higher figure (€11,955, mean: €12,639), followed by reteplase (€11,857, mean: €12,545) and then alteplase (€11,810, mean: €12,510), which shows that around 60% of the total patient lifetime treatment cost occurs in the first year post AMI.

Discussion

In Greece, the price of a new treatment is determined on the basis of simple computations of the product's prices in other countries and its reimbursement status is based on simple comparisons with the prices of drugs already included in the list. This is a limited approach to the evaluation of a new treatment and it ignores its overall economic impact on the health care system and society overall and the health benefit that it delivers per Euro spent in relation to its alternatives. We pursued an economic appraisal in this study to compare two widely used thrombolytic agents for the treatment of AMI patients with a new one, which has a marginally higher purchase price per dose and was thus excluded from the reimbursement list. It was shown that, for typical patients, the new agent has an overall treatment cost and cost-effectiveness similar to those already included in the list. In addition, it has advantages in large patient subgroups, in particular, the elderly above the age of 75 and late treated patients.

Thus, the study shows that the simple price comparisons used to make the decision not to include the new drug in the list are misleading and supports the opposite decision. Simple cross-country and cross-drug price comparisons are not sufficient to determine policies on whether or not to use certain treatments. Price and cost should always be considered and weighed against the economic and health benefit of the new treatment to patients and society. Economic evaluation and cost effectiveness analysis represent a means to quantify that benefit and to evaluate the trade-off. Despite their caveats and shortcomings, the former types of analysis can enable better informed decisions than simple price comparisons.

Study limitations

The analysis pursued suffers from drawbacks and limitations which are common in studies using similar methodologies. It does not represent experimental research, but instead it is based on a model populated from data reported in the literature and on various assumptions

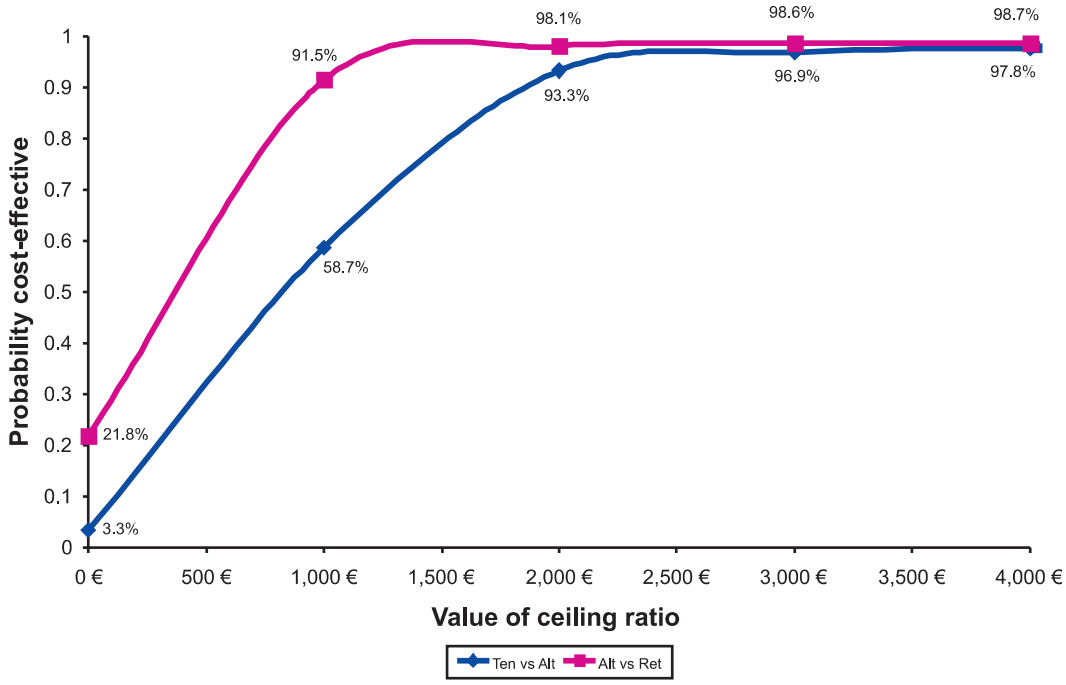

Figure 3. Cost effectiveness acceptability curve for patients treated after 4 hours.

and thus it may suffer from biases. To limit possible sources of bias, standard recommendations were followed. Thus, a systematic review and quality assessment of the evidence was performed and stochastic analysis was used to draw robust conclusions. This methodology, however, can not substitute for direct real life comparisons of cost-effectiveness between these treatments. The results have to be considered in the strict Greek NHS hospital setting and on the basis of the present time resource and drug prices. It should also be stressed that we did not consider the quality of life of patients, in other words we did not calculate quality-adjusted life years. However, disaggregated quality of life data per therapy, type of patient risk group and event type are not available. Nonetheless, there is no evidence and no reason to believe that the three treatments considered differ in terms of their impact on patient quality of life and thus this omission does not alter the conclusions of the study, especially also in light of the fact that the incremental ratios estimated were very low. Finally, we confined the analysis to the health care system and not society overall but this is because of the question in hand: that is, whether it is worth reimbursing tenecteplase within the context of the NHS. A broader analysis could be the scope of additional research as could, more importantly, a comparison between thrombolysis and angioplasty.

Acknowledgments

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